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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,346	09/23/2005	Fabrice Le Gall	03528.0146.PCUS00	7228

27194 7590 10/03/2008

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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,346	LE GALL ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3,4,9-12 and 14-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-8,13 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-7-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election and amendment in the reply filed on June 6, 2008 is acknowledged.

   Claim 1 has been amended.

   Claims 1-20 are pending.

2. Applicant's election with traverse of Group I in the he reply filed on June 6, 2008 is acknowledged. The traversal is on the ground(s) that Holliger does not disclose human (as amended in claim 1) anti-CD3 antibodies encompassed by the instant claims. This is not found persuasive because while Holliger may not explicitly disclose human anti-CD3 antibodies encompassed by the instant claims, it nevertheless would have been obvious for one of ordinary skill in the art to make a bivalent anti-CD3 diabody according to the teachings of Holliger given the common knowledge in the art of CD3 directed human immunotherapies and such an antibody would inherently be immunosuppressive.

   Accordingly, the requirement is still deemed proper and is therefore made FINAL.

   Applicant's election of the species of antibody which is the product of non-covalent dimerization or multimerization of single chain Fv antibodies wherein the antibody comprises two or more scFv antibodies wherein the Vh and Vl domains of each scFv are separated by peptide linkers or by no linkers in an orientation preventing their intramolecular pairing, i.e., the diabody format. is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

   Accordingly, the election of species requirement is still deemed proper and is therefore made FINAL.

   Applicant indicates that claims 1-8, 13 and 18-20 read on the elected species. The examiner agrees with applicant's assessment of the claims that read on the elected species but for claims 3 and 4. Claim 3 reads on species A and B while claim 4 reads on species D (see the Restriction Requirement mailed May 8, 2008).

   Accordingly, claims 3, 4, 9-12 and 14-17 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group or species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 6, 2008.

   Therefore, claims 1, 2, 5-8, 13, and 18-20 are under examination as they read on a bivalent or multivalent antibody characterized by the following features: (a) it is capable of suppressing an immune reaction; (b) it is devoid of constant antibody regions; and (c) it specifically binds to human TCR/CD3 complex, wherein the elected species of antibody is an antibody which

is the product of non-covalent dimerization or multimerization of single chain Fv antibodies wherein the antibody comprises two or more scFv antibodies wherein the Vh and Vl domains of each scFv are separated by peptide linkers or by no linkers in an orientation preventing their intramolecular pairing, i.e., the diabody format.

3. Claim 1 is objected to because "supressing" is a misspelling. The first paragraph of the specification is objected to because "Septmebre" is a misspelling.

   The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 5, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

   Claim 1 recites (emphasis added), "a bivalent or multivalent antibody characterized by the following features: (a) it is capable of suppressing an immune reaction; (b) it ***is devoid of constant antibody regions***; and (c) it specifically binds to human TCR/CD3 complex."

   Claim 5, which depends from claim 1, recites "[t]he antibody according to claim 1, wherein its variable VH and VL domains are connected via the peptide linker SAKTTP (SEQ ID NO: l) or SAKTTPKLGG (SEQ ID NO:2)."

   However, the instant specification does not define what is meant by the phrase "devoid of constant antibody regions." Moreover, this phrase, given its broadest reasonable interpretation consistent with the instant specification, reads on an antibody devoid of any recognizable constant antibody region sequence whatsoever. However, SEQ ID NOs: 1 and 2 of depended claim 5 are derived, at least in part, from the murine IgG1/IgG2b constant antibody regions as shown, for example, by Sheriff et al. (J Mol Biol. 1996 Nov 1;263(3):385-9, see Figure 1). Thus, it is unclear what applicant intends to claim.

   Furthermore, claims 7 and 8 refer to the "cysteine at position H100A" but do not put this nomenclature in the proper context, i.e., does this refer to Kabat numbering system or to some other antibody numbering system, such as one of the Chlothia numbering schemes?

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 5-8, 13, and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a bivalent antibody characterized by the following features: (a) it is capable of suppressing an immune reaction; (b) it is devoid of constant antibody regions; and (c) its two binding sites specifically bind human CD3 AND for a bivalent antibody characterized by the following features: (a) it is capable of suppressing an immune reaction; (b) it is devoid of constant antibody regions; and (c) its two binding sites specifically bind human CD3, wherein the variable domains of said antibody correspond to the variable domains of an antibody produced by the hybridoma of ATCC deposit number CRL 8001 and wherein a cysteine at position H100A according to the Kabat numbering scheme of said variable domains has been changed to a serine, ***does not reasonably provide enablement for*** a bivalent or multivalent antibody characterized by the following features: (a) it is capable of suppressing an immune reaction; (b) it is devoid of constant antibody regions; and (c) it specifically binds to human TCR/CD3 complex OR for a bivalent or multivalent antibody characterized by the following features: (a) it is capable of suppressing an immune reaction; (b) it is devoid of constant antibody regions; and (c) it specifically binds to human TCR/CD3 complex, wherein the variable domains of said antibody correspond to the variable domains of an antibody produced by the hybridoma of ATCC deposit number CRL 8001 and wherein a cysteine at position H100A according to the Kabat numbering scheme of said variable domains has been changed to another amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states on page 1404, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The level of skill in the art of making bivalent antibodies that bind CD3 monovalently and cause immunosuppression or of making multivalent antibodies that bind CD3 monovalently and cause immunosuppression or multivalent antibodies that bind CD3 bivalently and further bind one or more other ligands and cause immunosuppression or of making changes to a residue near the center of the OKT3 CDR-H3 with a degree of predictability and without adversely affecting antigen-binding abilities is low.

The instant specification exemplifies the production of a bivalent antibody characterized by the following features: (a) it is capable of suppressing an immune reaction; (b) it is devoid of

constant antibody regions; and (c) its two binding sites specifically bind human CD3, wherein the variable domains of said antibody correspond to the variable domains of an antibody produced by the hybridoma of ATCC deposit number CRL 8001, i.e., the OKT3 antibody, and wherein a cysteine at position H100A according to the Kabat numbering scheme of said variable domains has been changed to a serine (see entire specification, e.g., Figures 3 and 14).

However, with respect to making bivalent antibodies that bind CD3 monovalently and cause immunosuppression or of making multivalent antibodies that bind CD3 monovalently and cause immunosuppression or multivalent antibodies that bind CD3 bivalently and further bind one or more other ligands and cause immunosuppression, the instant specification provides no evidence of making such antibodies, the art does not support the notion that monovalent binding to CD3 would be sufficient to induce immunosuppression, and in fact the art is replete with evidence of bispecific anti-CD3 x anti-other ligand antibodies, e.g., anti-CD3 x anti-CD4 or anti-CD3 x anti-CD19, which act much like the FcR binding to whole anti-CD3 antibody to stimulate T-cells rather than suppress their activities (see, e.g., Smith et al. WO-9847531 in particular page 16, 96 and Little et al., 7129330, see, e.g., column 8, last paragraph).

The instant specification further discloses that the stability of an OKT3 scFv can be increased by mutagenesis of the cysteine at position H100A according to the Kabat numbering scheme to a serine and that this substitution does not adversely affect CD3 binding (see Instant specification, paragraph bridging pages 2-3).

However, the skilled artisan would be unable to predictably change the Cys residue at position H100A to any residue other than serine and be able to predict with any reasonable degree if the resulting antibody would bind the anti-CD3 antibody to the extent required to mediate the claimed immunosuppression.

For example, Kipriyanov et al. (Protein Eng. 1997 Apr;10(4):445-53) teaches on page 452, left column, 2nd paragraph that H100A lies in the middle of the OKT3 CDR-H3 antigen-combining site which generally has the greatest influence on antigen binding, that change to a hydrophobic residue could lead to a change in the CDR-H3 orientation and that "we are aware that, however that the substitution [of the Cys at H100A] might interfere with antigen binding or influence contact between the variable domains. Fortunately, the Cys to Ser mutation had no effect on antigen binding..."

Given the teachings of Kipriyanov it appears the skilled artisan would not have felt comfortable predicting which amino acid changes to H100A would be have significant effect on antigen binding. Moreover, the teachings of Kipriyanov do not support the notion that the skilled artisan would consider making and testing the remaining 18 amino acid substitutions in the context of the OKT3 scFv antibody to be a matter of simple experimentation.

Consistent with the teachings of Kipriyanov put forth above, MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745), analyzed many different antibodies for interactions with antigen and state that the light and heavy chain CDR3 regions dominate, and a further uncertainty about which residues are most important in CDR-H3-antigen binding come from its length variability (paragraph bridging columns on page 733).

As a further example of the unpredictability of making changes to the sequence of an antibody is provided by Rudikoff et al. (Proc. Natl. Acad. Sci. USA, 79: 1979-1 983, March 1982, cited previously), who teaches that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. In particular, Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function (see, for example, Abstract). Similarly, Colman P. M. (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column).

In conclusion, the instant claims encompass an invention of substantial breadth, and essentially call for trial and error by the skilled artisan to begin discovering how to make the claimed invention without assisting the skilled artisan in such an endeavor, which is insufficient to constitute adequate enablement.

The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Undue experimentation would be required to produce the invention commensurate with the breadth of the claims based on the disclosure of the instant specification and the knowledge in the art. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

It is noted for the record that the hybridoma ATCC deposit number CRL 8001 was known and readily available to the public as of applicant's date of invention and is still known and readily available currently.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1, 2, 13, 18-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Digan et al. (US20020142000).

The instant claims read on a bivalent or multivalent anti-CD3 antibody that is immunosuppressive and devoid of constant antibody regions. One embodiment of the instant specification is a diabody, as in claim 2. The instant specification does not define or limit what is meant by "an antibody" as recited in the instant claims. This phrase, given its broadest reasonable interpretation consistent with the instant specification and with its plain meaning in the art, reads on any polypeptide molecule comprising Vh and Vl immunoglobulin variable domains that bind CD3 antigen. In this respect the phrase "an antibody" refers to a genus of molecules that comprise Vh and Vl immunoglobulin variable domains that bind CD3 antigen.

Digan teaches an anti-CD3 diabody which comprises Vh and Vl immunoglobulin variable domains that bind CD3 antigen, and further comprises a polypeptide based toxin derived from Pseudomonas aeruginosa, and pharmaceutical compositions thereof (see, e.g., Digan Figure 16B, page 8, paragraph [0126]; page 17, paragraph [0287] to page 18, paragraph [0307] and Abstract).

Thus, Digan teaches a species of antibody, i.e., an anti-CD3 diabody which comprises Vh and Vl immunoglobulin variable domains that bind CD3 antigen, and further comprises a polypeptide based toxin derived from Pseudomonas aeruginosa and pharmaceutical compositions thereof that anticipate the instant claims.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 2, 6, 13 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 9847531) in view of Hsu et al. (Transplantation. 1999 Aug 27;68(4):545-54), Holliger et al. (5,837,242) and Chapman et al. (Nat Biotechnol. 1999 Aug;17(8):780-3).

Smith teaches that FcR-nonbinding anti-CD3 antibodies, including $F(ab')_2$ anti-CD3 antibodies, are potent immunosuppressants which have a variety of uses in treating autoimmune diseases and graft rejection. According to Smith such antibodies lack the first-dose reaction attributable to anti-CD3 FcR mediated crosslinking as occurs clinically with the

intact anti-CD3 antibody OKT3 (see Smith, e.g., the sentence bridging pages 14-15; pages 17-23 and claims 2 and 6). Smith also teaches that anti-CD3 therapeutic antibodies can be prepared, for example, as sterile injectable compositions (see Smith, e.g., page 57, 2nd and 3rd paragraphs).

Smith further teaches the following at page 50, 2nd paragraph:

"As a therapeutic drug, a major problem associated with OKT3 is the first-dose reactions attributed to the T cell activation by the mAb. These properties are not removed by forming a humanized OKT3 monoclonal antibody. Since gOKT3-5 produces, in vitro, similar activation to OKT3, it is quite likely that the same side-effects might also occur with this drug in vivo. $F(ab')_2$ fragments of OKT3 have led to potent immunosuppression and TCR modulation, in vitro. Non-activating $F(ab')_2$ fragments of anti-CD3 mAbs to mice was as efficacious as whole anti-CD3 in delaying skin graft rejection, while the $F(ab')_2$ fragments exhibited significantly reduced T cell activation and fewer side-effects in mice. However, the production of $F(ab')_2$ fragments in large quantities remains difficult. Furthermore, the half-life of this drug in the blood stream is relatively short, as compared with whole mAb. Thus, frequent injections of the $F(ab')_2$ fragments of anti-CD3 were necessary to achieve maximal immunosuppression, making the use of this mAb fragment inappropriate for clinical transplantation. Finally, recent studies have shown that even a small contaminant of whole mAb in the F(ab') preparation ($<1/10^4$ molecules) has a synergistic effect on T cell activation."

Thus, Smith teaches that while non-activating $F(ab')_2$ fragments of anti-CD3 mAbs are fully efficacious in a mouse model and de facto lack the FcR binding portion of the antibody constant domain, these antibodies nonetheless suffer from a number of drawbacks such as lower serum half-life compared to whole mAb, the difficulty of making large quantities and the potential for whole mAb contamination, presumably when these molecules are prepared via pepsin digestion of whole mAbs. The solution that Smith provides for these challenges is to teach the production of whole anti-CD3 antibodies having various mutations in the Fc CH2 region, such as mutations in residues 234 and 235 of Fc CH2 which decrease the ability of the mutated anti-CD3 antibody to bind FcR (see Smith, e.g., page 50, 3rd paragraph to page 53).

Smith differs from the claimed invention in that Smith does not explicitly teach that a diabody can be used in place of, for example, a whole anti-CD3 antibody containing Fc mutations or an anti-CD3 $F(ab')_2$.

However, the teachings of Hsu demonstrate that a humanized anti-CD3 antibody having mutations in residues 234-237 of the Fc CH2 region when administered to a chimpanzee while being far less mitogenic nevertheless stimulates significant proinflammatory cytokine release upon administration. While Hsu does teach that this effect could be a peculiarity of the response of the chimpanzee immune system to the Fc modified antibody, the teachings of Hsu nonetheless illustrate the caveats associated with using an intact anti-CD3 antibody

having Fc mutations rather than using an anti-CD3 antibody devoid of constant antibody regions (see Hsu, e.g., page 14, penultimate paragraph to page 15, 1st paragraph).

One of ordinary skill in the art would recognize a solution to this dilemma in the teaching of Holliger that a bivalent anti-CD3 diabody can be used to cross-link CD3 while at the same time being devoid of antibody FcR binding regions, unlike the antibody of Hsu (see Holliger, e.g., column 22, 1st paragraph and column 2, last paragraph to column 4).

Furthermore, unlike anti-CD3 $F(ab')_2$ antibodies, as would be obvious to one of ordinary skill in the art, the production of diabodies does not carry with it the risk of whole antibody contamination. Moreover, Holliger teaches methods of extending the stability of diabodies via various mutations to increase the strength of chain to chain interactions as well as diabody purification procedures (see Holliger, column 17, last paragraph to column 19).

Furthermore, additional methods of increasing the serum stability of antibody fragments such as scFv, e.g., via pegylation, were known in the art as of applicant's date of invention. For example, Chapman teaches that a Cys containing hinge region attached to the C terminus of an scFv would allow for PEG attachment to the antibody fragment to increase serum stability without any loss in antigen binding expected (see Chapman, e.g., page 782, left column, 1st paragraph). Chapman further teaches additional advantages of antibody fragments vs. whole antibodies for therapeutic use, such as cost and time efficient production (see Chapman page 780, left column, 1st paragraph and page 782, left column, 2nd and 3rd paragraphs).

Thus, given the reference teachings and the knowledge in the art as of applicant's date of invention, it would have been obvious to one of ordinary skill in the art that a bivalent anti-CD3 OKT3-based diabody can be used as an immunosuppressant in the same way that a bivalent anti-CD3 OKT3-based $F(ab')_2$ can be used as an immunosuppressant.

Importantly, both anti-CD3 diabody and anti-CD3 $F(ab')_2$ antibodies are devoid of the antibody constant regions which mediate FcR cross-linking, thus one of ordinary skill in the art would have been motivated to make and use such molecules for therapeutic uses vs. a whole anti-CD3 antibody since the caveats associated with attempting to inhibit FcR cross-linking through point mutagenesis of antibody Fc are not an issue. Additionally, as taught by Chapman, compared to whole antibodies, antibody fragments allow for decreased cost and time to production so this is an additional motivation one of ordinary skill in the art would have for making, for example, an anti-CD3 diabody vs. a whole antibody containing a mutation in the Fc region that inhibits FcR cross-linking.

One of ordinary skill in the art would have been motivated to make an anti-CD3 diabody in particular because, unlike the bivalent anti-CD3 $F(ab')_2$, the bivalent anti-CD3 diabody does not run the risk of being contaminated with intact antibodies. Furthermore, given that large-scale cost efficient production is possible with Fab', Fv and scFv according to Chapman, one of ordinary skill in the art, filtered through their knowledge of the art, would readily surmise that large-scale cost efficient production of a diabody would also be reasonable, in contrast to

the teachings of Smith regarding the difficulty of producing large quantities of $F(ab')_2$ fragments.

Furthermore, the teachings of Holliger regarding ways to stabilize diabodies via site-specific mutagenesis, and the teachings of Chapman regarding ways to stabilize antibody fragments in general via pegylation, would have given one of ordinary skill in the art additional motivation to make such a molecule knowing that it could be used not only in vitro but also in vivo.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Smith in view of Hsu, Holliger and Chapman.

12. Claims 1 and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 9847531) in view of Hsu et al. (Transplantation. 1999 Aug 27;68(4):545-54), Holliger et al. (5,837,242) and Chapman et al. (Nat Biotechnol. 1999 Aug;17(8):780-3) as applied to claims 1, 2, 6, 13 and 18-20 above, and further in view of Kipriyanov et al. (Protein Eng. 1997 Apr;10(4):445-53).

The teachings of Smith, Hsu, Holliger and Chapman are given in Section 11 above.

In addition, it is noted that Holliger teaches that "[w]here one is seeking to convert a particular cloned antibody into a diabody format, it is a simple matter to vary the linker length (e.g. from 0 upwards) to see what works best. Likewise, substitution of different linkers, even of the same length, may be advantageous." (see Holliger column 16, 2nd paragraph). In this regard, Holliger teaches that linkers of length anywhere from 0-9 amino acids allow the production of diabodies although linkers of 10 amino acids or more can be used if they are subject to "limiting structural features" which serve to decrease their effective length (see Holliger, e.g., column 3, 5th paragraph). Holliger further teaches that one source of starting material for a diabody is a cloned scFv (see Holliger, e.g., column 3, 5th paragraph; column 27, 5th paragraph and Example 1, columns 31-35).

However, Smith, Hsu, Holliger and Chapman do not explicitly teach the use of the particular linker SEQ ID NOs: 1 to connect the Vh and Vl domains or mutagenesis of the cysteine at H100A to serine according to the Kabat number system of OKT3.

Nevertheless, Kipriyanov teaches that bacterial production of an OKT3 scFv can be increased by mutagenesis of the cysteine at position H100A (according to the Kabat numbering scheme) to a serine and that this substitution does not adversely affect CD3 binding (see Kipriyanov, e.g., page 452, left column). Moreover, Kipriyanov teaches that

their OKT3 scFv contains a 17 amino acid peptide linker "AKTTPKLEEGEFSEARY" which is preceded by a Ser residue.

Given the reference teachings, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to shorten the linker already present in the anti-OKT3 scFv of Kipriyanov to make an OKT3 diabody given that this linker sequence had a proven ability to be part of an scFv which was efficiently expressed in bacteria. Moreover, given the reference teachings it would have been obvious to one of ordinary skill in the art that SEQ ID NOs: 1 of the instant claims, i.e., "SAKTTP," is one of a finite number of possible, and equally reasonable, linker sequences that could be used to generate a OKT3 diabody using the OKT3 scFv of Kipriyanov as the starting material.

Furthermore, with respect to preparing an OKT3 based diabody comprising a serine mutation at Kabat position H100A in place of the Cys found in the parent antibody, one of ordinary skill in the art would have been motivated to make such a change given the teachings of Kipriyanov that this particular substitution increases bacterial production of an OKT3 scFv without adversely affecting CD3 binding.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Smith in view of Hsu, Holliger, Chapman and Kipriyanov.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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